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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
KAUFMAN, CLAIRE M

ART UNIT	PAPER NUMBER
1646	

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34

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/042,583	NI, ET AL.	
	Examiner	Art Unit	
	Claire M. Kaufman	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *6/4/02, 7/1/02* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *287-622* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *see continuation* is/are allowed.

6)☒ Claim(s) *see continuation* is/are rejected.

7)☒ Claim(s) *see continuation* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *28* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

Continuation of Form 326, Paper #34

Disposition of Claims

5) Claims 300-318, 340-350, 374-388, 416-430, 459-475 and 595-607 are allowed.

6) claims 287-299, 319, 326-339, 351, 353-373, 389, 391-415, 431, 433-458, 476, 478-565, 567-594 and 608-622 are rejected.

7) Claims 320-325, 352, 390, 432, 477 and 566 are objected to.

DETAILED ACTION

The amendment filed 6/4/02 has been entered.

Applicants change of address is now correct in the USPTO system for Customer Number 28730.

Response to Amendment

The rejection of claims under 35 USC 112, second paragraph, is withdrawn in view of the amendment to the claims.

The rejection of claims 404-415, 418 and 433 under 35 USC 112, first paragraph, is withdrawn in view of the amendment to the claims. Note that other claims still remain rejected.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Declaration

The Declarations filed on 6/4/02 and 7/1/02 under 37 CFR 1.131 have been considered but is ineffective to overcome the US Patent 6,072,074 reference.

The evidence submitted is insufficient to establish a reduction to practice of the invention in this country or a NAFTA or WTO member country prior to the effective date of the US Patent 6,072,074 reference. The data for clone HLYBX88 shows only nucleotides 1080-1200 of SEQ ID NO:1of the instant application (encoding 40 amino acids). Patent 6,072,074 shows 50 encoded amino acids, which are encoded by nucleotides 148-1200 of SEQ ID NO:1 of the instant application. Nor was there evidence of conception of the fragment as part of a protein that induced apoptosis.

Further, according to MPEP 715.04, the following parties may make an affidavit or declaration under 37 CFR 1.131:

(A) All the inventors of the subject matter claimed.

(B) An affidavit or declaration by less than all named inventors of an application is accepted where it is shown that less than all named inventors of an application invented the subject matter of the claim or claims under rejection. For example, one of two joint inventors is accepted where it is shown that one of the joint

inventors is the sole inventor of the claim or claims under rejection.

(C) A party qualified under 37 CFR 1.42, 1.43, or 1.47 in situation where some or all of the inventors are not available or not capable of joining in the filing of the application.

(D) The assignee or other party in interest when it is not possible to produce the affidavit or declaration of the inventor. Ex parte Foster, 1903 C.D. 213, 105 O.G. 261 (Comm'r Pat. 1903).

The declaration is deficient because it is not signed by Inventor Ni, and it has not been shown that fewer than all the inventors invented the claimed subject matter currently rejected.

Claim Objections

Claim 433 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. What is being replaced is the same thing as that which it is being replaced. It appears you end up with the exact thing with which you started.

Claim Rejections - 35 USC § 112, Second Paragraph

Claim 494 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 494 as amended recites the limitation "said 30 contiguous amino acids" in lines 3-4. There is insufficient antecedent basis for this limitation in the claim. The claim from which it depends, 492, recites 30 contiguous nucleic acids.

Claim Rejections - 35 USC § 112, First Paragraph

Claims 494, 522, 540, 609 and 610 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for (1) an isolated polynucleotide comprising a nucleic acid which encodes a polypeptide (a) consisting of an amino acid sequence at least 90% identical to amino acids 1-133 of SEQ ID NO:2 (*i.e.*, the ECD of DR5), wherein said polypeptide

binds TRAIL or (b) consisting of an amino acid sequence at least 90% identical to amino acids 158-360 of SEQ ID NO:2 (*i.e.*, the ICD of DR5), wherein said polypeptide induces apoptosis *in vitro* when over-expressed in human 293 embryonic kidney cells, or (2) an isolated polynucleotide comprising a nucleic acid which encodes a polypeptide fragment at least 90% identical to amino acids 273-340 of SEQ ID NO:2, and wherein a DR5 variant consisting of amino acids 1 to 360 of SEQ ID NO:2, with the exception that amino acids 273-340 of SEQ ID NO:2 are deleted and replaced with said polypeptide fragment, induces apoptosis *in vitro* when over-expressed in human 293 embryonic kidney cells, does not reasonably provide enablement for (1) the claimed polynucleotide comprising a nucleic acid which encodes a polypeptide (a) consisting of an amino acid sequence less than 90% identical to amino acids 1-133 of SEQ ID NO:2, which includes sequences smaller than 90% of the length of the full ECD of DR5, wherein said polypeptide must binds TRAIL or (b) consisting of an amino acid sequence less than 90% identical to amino acids 158-360 of SEQ ID NO:2, which includes sequences smaller than 90% of the length of the full ICD of DR5, wherein said polypeptide induces, or (2) an isolated polynucleotide comprising a nucleic acid which encodes a polypeptide fragment at least 90% identical to amino acids 273-340 of SEQ ID NO:2 or a 5-50 contiguous amino acid-long fragment of SEQ ID NO:2 from amino acids 1-360 or 158-360 of SEQ ID NO:2 which induces apoptosis. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims for the reasons set forth in the previous Office action (paper #34).

Applicants argue that the claims have been amended to indicate substitution with a function, so they are now enabled. The argument has been fully considered, but is not persuasive. For claim 494, 30 contiguous amino acids are being substituted for another 30 contiguous amino acids, but not necessary the corresponding ones. For example, amino acid residues 1-30 could be deleted and substituted with amino acid residues related to 330-360. The functionality of such a variant would be unpredictable. For claim 522, a fragment of over 150 amino acids long (158-360 of SEQ ID NO:2) is being substituted by a 5 amino acid long fragment, which is not enabled as previous discussed. For claim 540, a fragment 90% identical to 30 amino acids is being substituted for a fragment over 150 amino acids long, which is not enabled as previous discussed. Claims 609 and 610, like claim 494, have a substitution of, in these claims, 50

contiguous amino acids with another 50 contiguous amino acids from SEQ ID NO:2, however, there is no limitation concerning which 50 contiguous amino acids are removed and which 50 contiguous are added.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) do not apply to the examination of this application as the application being examined was not (1) filed on or after November 29, 2000, or (2) voluntarily published under 35 U.S.C. 122(b). Therefore, this application is examined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claims 492-495, 507-508, 518-523, 535-541 and 608-611 remain rejected under 35 U.S.C. 102(e) as being anticipated by US Patent No. 6,072,047, cited by Applicants, for the reasons set forth in the previous Office action on page 7.

US Patent No. 6, 072,047 receives priority back to March 12, 1997 (application number 08/815,255) for the DNA fragment encoding the TRAIL-R fragment in Figure 1 of the patent, which is the same as amino acids 336-386 of SEQ ID NO:2 of the patent. This TRAIL receptor fragment is identical to amino acids 256-306 of SEQ ID NO:2, which is encoded by nucleotides 1048-1200 of SEQ ID NO:1, of the instant application. The DNA fragment was obtained after the mature protein had been purified (EXAMPLE 1 and 2) by using degenerate oligonucleotide primers (heterologous polynucleotides) for PCR (EXAMPLE 3). As later shown in US Patent 6,072,047, the above fragment functions within a mature DR5 to induce apoptosis.

Note that even with the amendment to claims reciting substitution in a DR5 variant, the claimed polynucleotide still appears to be the same as that of the patent relied upon above.

Additionally, it is noted that the claims are not drawn to a variant but to a polynucleotide encoding a fragment. Also, as discussed in the response to the rejection under 35 USC 112, first paragraph, some of recited variants do *not* have to be functionally or structurally different from wildtype/disclosed DR5.

Applicants argue that the Declaration under 37 CFR 1.131 by Ni et al. establishes that the inventors were in possession of the claimed invention prior to March 12, 1997. The argument has been fully considered, but is not persuasive. For the reasons discussed in the section bridging pages 2-3 of this Office action, the Declaration is not effective to overcome the rejection.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 492-552 and 608-622 remain rejected under 35 U.S.C. 103(a) as being unpatentable over US Patent No. 6,072,047, for the reasons set forth in the previous Office action on pages 8-9.

US Patent No. 6, 072,047 receives priority back to March 12, 1997 (application number 08/815,255) for the DNA fragment encoding the TRAIL-R fragment in Figure 1 of the patent, which is the same as amino acids 336-386 of SEQ ID NO:2 of the patent. This TRAIL receptor fragment is identical to amino acids 256-306 of SEQ ID NO:2, which is encoded by nucleotides 1048-1200 of SEQ ID NO:1, of the instant application. The DNA fragment was obtained after

the mature protein had been purified by affinity purification with TRAIL (TNF-Related Apoptosis-Inducing Ligand; EXAMPLE 1 and 2) by using degenerate oligonucleotide primers (heterologous polynucleotides) for PCR (EXAMPLE 3). TRAIL receptors binds TRAIL), which had been demonstrated to induce apoptosis in some cancer cells as well as virally infected cells (col. 1, lines 15-22). As later shown in US Patent 6,072,047, the above fragment functions within a mature DR5 to induce apoptosis.

Also taught are methods and means for recombinant cloning and expression vectors containing the TRAIL-R DNA, including: "A method of producing TRAIL-R polypeptides comprising culturing host cells transformed with a recombinant expression vector encoding trail-R, under conditions that promote expression of TRAIL-R, then recovering the expressed TRAIL-R polypeptides from cultures." (col. 8, lines 6-22) The encoding DNA may be operably linked to a suitable regulatory sequence (col. 8, lines 23-40). Also, how to make a polynucleotide encoding fusion protein of TRAIL-R and human Ig Fc region fusion protein in order to make TRAIL-R dimers (col. 13, lines 3—35). Such dimmers are useful for "facile purification by affinity chromatography over Protein A or Protein G columns" (col. 14, lines 9-14 and col. 15, lines 16-22). US Patent No. 6,072,047 does not teach the actually made products of this paragraph.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to make a polynucleotide comprising the TRAIL-R DNA fragment operably linked to a heterologous regulatory sequence as well as a heterologous polynucleotide sequence that encoded a human Ig Fc domain, and a method of making such, as taught by US Patent No. 6,072,047 for well known and suggested purposes of DNA amplification and protein production and purification. Because the DNA fragment of Figure 1 had been identified as encoding part of a TRAIL receptor, one would have been motivated to produce the above described products to characterize aspects of the receptor that binds TRAIL, which was known to be involved in apoptosis and have clinical implications. For these reasons, the invention is *prima facie* obvious.

Applicants argue that the Declaration under 37 CFR 1.131 by Ni et al. establishes that the inventors were in possession of the claimed invention prior to March 12, 1997. The argument has been fully considered, but is not persuasive. For the reasons discussed in the section

bridging pages 2-3 of this Office action, the Declaration is not effective to overcome the rejection.

Claims 287-299, 319, 326-339, 351, 353-373, 389, 391-415, 431, 433-458, 476, 478-491, 553-565 and 567-594 remain rejected under 35 U.S.C. 103(a) as being unpatentable over US Patent No. 6,072,047, for the reasons set forth in the previous Office action on pages 9-11.

US Patent No. 6, 072,047 receives priority back to Feb. 13, 1997 (application number 08/799,861) for the isolated mature TRAIL-R protein (SEQ ID NO:2 of patent). US Patent No. 6, 072,047 receives priority back to March 12, 1997 (application number 08/815,255) for the DNA fragment encoding the TRAIL-R fragment in Figure 1 of the patent, which is the same as amino acids 336-386 of SEQ ID NO:2 of the patent. This TRAIL receptor fragment is identical to amino acids 256-306 of SEQ ID NO:2, which is encoded by nucleotides 1048-1200 of SEQ ID NO:1, of the instant application. The DNA fragment was obtained after the mature protein had been purified by affinity purification with TRAIL (TNF-Related Apoptosis-Inducing Ligand; EXAMPLE 1 and 2) by using degenerate oligonucleotide primers (heterologous polynucleotides) for PCR (EXAMPLE 3). TRAIL receptors binds TRAIL, which had been demonstrated to induce apoptosis in some cancer cells as well as virally infected cells (col. 1, lines 15-22). As prophetically stated in priority application 08/799,861 and later shown in US Patent 6,072,047, the above fragment is part of and functions within a mature TRAIL-R to induce apoptosis. The mature TRAIL-R has a sequence identical to amino acids +1 to +360 of SEQ ID NO:2 of the instant application with the exception that TRAIL-R contains 29 additional amino acids inserted after amino acid residue 131 of SEQ ID NO:2 of the instant application. It is explained in col. 6, lines 6-19, that the TRAIL-R (or fragment thereof) may be encoded by a sequence degenerate to the native sequence of SEQ ID NO:1.

Also taught are methods and means for recombinant cloning and expression vectors containing the TRAIL-R DNA, including: "A method of producing TRAIL-R polypeptides comprising culturing host cells transformed with a recombinant expression vector encoding TRAIL-R, under conditions that promote expression of TRAIL-R, then recovering the expressed TRAIL-R polypeptides from cultures." (col. 8, lines 6-22) The encoding DNA may be operably linked to a suitable regulatory sequence (col. 8, lines 23-40). Also, how to make a

polynucleotide encoding fusion protein of TRAIL-R and human Ig Fc region fusion protein in order to make TRAIL-R dimers (col. 13, lines 3—35). Such dimmers are useful for "facile purification by affinity chromatography over Protein A or Protein G columns" (col. 14, lines 9-14 and col. 15, lines 16-22). US Patent No. 6,072,047 does not teach the actually made products of this paragraph.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to make a polynucleotide comprising a TRAIL-R polynucleotide or fragment operably linked to a heterologous regulatory sequence as well as a heterologous polynucleotide sequence that encoded a human Ig Fc domain, and a method of making such, as taught by US Patent No. 6,072,047 for well known and suggested purposes of DNA amplification and protein production and purification. Note that the encoding polynucleotide does not have to have the native sequence which encodes TRAIL disclosed in the patent. With the well known knowledge of the degeneracy of the genetic code, one of ordinary skill in the art could have readily envisioned all degenerate sequences that encoded the TRAIL-R protein without knowing what the actual native sequence was. This knowledge was the basis of making the degenerate oligo primers of US Patent 6,072,047 that allowed TRAIL-R DNA to be obtained. One would have been motivated to produce the above described products including polynucleotides encoding the mature TRAIL-R as well as fragments to characterize aspects of the receptor that binds TRAIL, which was known to be involved in apoptosis and have clinical implications. It is further noted that "comprising" is open language and when used in a claim before a fragment, allows from more amino acids or nucleic acids, as the case may be, than recited in the specific fragment. For these reasons, the invention is *prima facie* obvious.

Applicants argue that the Declaration under 37 CFR 1.131 by Ni et al. establishes that the inventors were in possession of the claimed invention prior to March 12, 1997. The argument has been fully considered, but is not persuasive. For the reasons discussed in the section bridging pages 2-3 of this Office action, the Declaration is not effective to overcome the rejection.

Applicants argue (bridging pages 17-18 of response) that the Feb. 13, 1997 priority document is insufficient to sustain a *prima facia* case on its own because it does not suggest the

invention or provide a reasonable expectation of success since the priority document disclosed protein and the instant claims are drawn to polynucleotides, and additionally because 2/3 peptides fragments disclosed in the Feb. 13, 1997 document were not usable to isolate the TRAIL receptor ultimately relied on. The argument has been fully considered, but is not persuasive. The priority document of Feb .13, 1997, was not relied upon alone for establishing US Patent 6,072,047 ('047), as prior art for the claimed invention. It may be true that the 2/13/97 document alone cannot support the obviousness rejection, as Applicants argue, but it was not relied upon alone as the basis for the rejection. Nevertheless, the information provided in both priority documents of 2/13/97 and 3/12/97 of the '047 patent establish that at least by 3/12/97 the information required to make obvious the instant invention was present so that the '047 receives priority back at least to the March date as a prior art reference relied upon under 35 USC 103. Therefore, taken together, and as synthesized in '047, it is maintained that the '047 patent relied upon makes obvious the claimed invention for the reasons set forth in the previous Office action

Art of Record

Applicants have made US Patent 6,342,369 of record in IDS paper #28. This patent is not available as prior art. It is also noted that amino acids 32 and 410 are different between SEQ ID NO:2 of the patent and the instant application. US Patent 6,313,269, also made of record in #28, receives benefit for effective filing date of Provisional Application 60/041,230, filed 3/14/97, which teaches amino acids +58 to 411 of SEQ ID NO:2 of the instant application, which is called amino acids 109-360 of the instant claims of SEQ ID NO:2 of the instant application, in the patent priority document of 3/14/97. While this patent is available as prior art, it is cumulative with that already relied upon. Additionally, it is noted that amino acid 106 is different between SEQ ID NO:2 of the patent and the instant application. The species claimed in the patents are not obvious in light of the instant claims.

Conclusion

Claims 300-318, 340-350, 374, 375-388, 416-430, 459-475 and 595-607 are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Claire M. Kaufman, whose telephone number is (703) 305-5791. Dr. Kaufman can generally be reached Monday through Thursday from 8:30AM to 12:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler, can be reached at (703) 308-6564.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Official papers filed by fax should be directed to (703) 308-4242. Faxed draft or informal communications with the examiner should be directed to (703) 308-0294. NOTE: If applicant *does* submit a paper by fax, the original signed copy should be retained by the applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office. **Please** advise the examiner at the telephone number above before facsimile transmission.

Claire M. Kaufman, Ph.D.
Patent Examiner, Art Unit 1646
August 19, 2002

Gary L. Kunz